

REMARKS

Claims 77-101 are pending in this application. Claims 97 and 98 have been amended merely to correct claim dependencies. Claims 77-101 were previously indicated as allowable and this application was withdrawn from issue by the Office after payment of the issue fee. Applicants note with appreciation that the Office continues to hold the issue fee and will apply it to any subsequent issue fee due in this case or refund the full amount upon Applicants' request.

Applicants respectfully assert that this paper is fully responsive to the outstanding Final Action and satisfies the submission requirement under 37 CFR 1.114 for the accompanying Request for Continued Examination (RCE).

35 U.S.C. § 101

Claims 77-101 stand rejected for allegedly lacking support by "either a specific and substantial asserted utility or a well established utility." The rejection was maintained for reasons of record in the March 21, 2003 and March 18, 2005 Office Actions.

Applicants respectfully direct the examiner's attention to MPEP § 2107 I which states:

If the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the *prima facie* showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained.

Thus, the utility rejection can be maintained only if the totality of the record shows the utility is not specific, substantial and credible.

The Office's prior reasoning was maintained and we turn to the March 18, 2005 Office Action, at page 6, where the Action notes that

compounds that specifically activate or inhibit hARE-2 are not disclosed and neither are diseases associated with hARE-2 dysfunction disclosed. Furthermore, the specification fails to disclose ligands that bind or activate hARE-2. Each clinical agent, which has been developed by measuring its interaction with a specific GPCR was evaluated against a receptor whose native ligand and physiological function were known, such as the adrenergic receptors, the dopamine receptors and the serotonin receptors. There are also numerous GPCRs, such as the odorant receptors, which do not mediate any clinically significant process. More importantly, the artisan knew, before they employed a specific GPCR to identify clinically useful compounds, which physiological process or processes they wished to manipulate and that the receptor protein employed in their assay had an influence of that process. Even if one identifies an agonist or antagonist for a receptor of the instant invention, this information is useless since one has no idea of what clinical effect the administration of that agonist or antagonist to an individual would have.

There is no requirement for Applicants to disclose compounds that specifically activate or inhibit hARE-2 or diseases associated with hARE-2 dysfunction. Because a well-established utility satisfies the requirement under 35 U.S.C. § 101, these can come from the knowledge in the art, if needed. While it may be true that other clinical agents have been identified where a ligand is known, the Office has neither provided any evidence to support the truth of the implication that such a ligand must be known, nor does the Action point to any rule requiring that such a ligand be known to establish utility. Additionally, the fact that other GPCRs do not mediate any clinically significant process does not mean that hARE-2 does not and, therefore, indication of such is not probative of the issues at hand. The Office notes that numerous GPCRs, such as the odorant receptors, do not mediate any clinically significant process. However, the Office has not provided any evidence that such receptors are expressed in the substantia nigra, as is hARE-2, and therefore are not indicative that a GPCR expressed in the substantia nigra would not be clinically significant. Further, no one of skill in the art would confuse hARE-2 with an olfactory or "odorant" receptor because, for example, hARE-2 lacks the VAICXXL motif in IC2 and the KXXSTC motif in IC3 uniquely conserved in olfactory receptors (see, e.g., the legend to Figure 1(a) in Pilpel et al, *Essays Biochem* (1998) 33:93-104). Finally, although the Action

indicates that Applicants have not set forth any indication that hARE-2 would have an influence on any process, those of skill in the art would have, at the time of filing, recognized such an influence as detailed below. Applicants respectfully assert that the totality of the record clearly indicates a well-established utility, namely the use of hARE-2 for treating disorders of the substantia nigra, such as Parkinson's disease.

The record clearly shows that:

A. Applicants have disclosed:

1. hARE-2 is a GPCR, see e.g. p. 17, line 18 of the original disclosure;
2. GPCRs affect the level of cAMP or IP₃ in a cell, see p. 12, line 2 to p. 13, line 16 of the original disclosure, see also supporting Graph 1 filed September 19, 2003;
3. hARE-2 is expressed in the substantia nigra, see, e.g. Table C, page 27 of the original disclosure; and that

B. those of skill in the art, at the time of filing, would have known:

1. GPCRs affect the level of cAMP or IP₃ in a cell. See, e.g. Lambert (1993) Br J Anaesth 71:86-95 (pp. 86-90, Fig. 1 at p. 87);
2. an elevation of intracellular IP₃ leads to an elevation of intracellular Ca²⁺. See, eg. Berridge (1993) Nature 361:315-325;
3. Parkinson's disease is caused by a loss of neurons in the substantia nigra. See e.g. Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), McGraw-Hill (p. 504, lines 6-10, left column) and Blaszczyk 91998) Acta Neurobiol Exp (Wars) 58:79-93 (see Abstract lines 12-14), and Montastruc et al (1996) Drugs Aging (:169-184 (p. 170, line 47, left column to line 2 right column); and
4. viability of neurons in the substantia nigra is affected by the level of cAMP in a cell and by the level of Ca²⁺ in a cell. See, for example, Hulley et al (1995) European Journal of Neuroscience 7:2431-2440 and Hirsch et al (1997) J Neural Transm Suppl 50:79-88.

The fact that hARE-2 influences the viability of neurons in the substantia nigra is supported by the data previously submitted in Graph 1, which clearly indicates that hARE-2 influences cAMP levels. It should be noted that the experiment depicted in Graph 1 was conducted with routine procedures by one skilled in the art and did not require any undue effort. As noted above, those of skill in the art recognized cAMP levels affect the viability of neurons, which is a known factor in Parkinson's. Thus, the totality of the evidence, including Applicants' disclosure, the knowledge of those of skill in the art at the time of filing, as evidenced by the references made of record, and Applicants' supporting graphical data all point to the fact that those of skill in the art would recognize a well-established utility for hARE-2.

Given Applicants' disclosure, and the knowledge of one of ordinary skill in the art, logic dictates that there is a well-established utility for treating Parkinson's disease, since hARE-2 is a GPCR expressed in the substantia nigra affecting cAMP or Ca^{2+} levels in the cells which are known to affect neuron viability, a known factor in Parkinson's disease. This utility is specific to hARE-2, is substantial in that it treats a real world disorder, and credible, as admitted to on page 8 of the Action ("there is no issue with the credibility of the asserted utility"). Previously, Applicants submitted a graph showing that hARE-2 expression does, in fact, result in a decrease in cAMP, thus confirming (not asserting) Applicants' position that hARE-2 affects cAMP levels which in turn affect neuron viability.

Absent any evidence from the Office to contradict Applicants' disclosure or the knowledge of those of ordinary skill in the art, the totality of the record clearly indicates that those of ordinary skill in the art would have recognized a well-established utility. For this reason alone, the utility rejection should be withdrawn.

Although we maintain the well-established utility would be recognized by those of skill in the art, Applicants respectfully assert that the Application as filed asserts a specific, substantial, and credible utility.

Applicants respectfully assert that the above discussion is sufficiently clear and dispositive of the utility issue. Nevertheless, Applicants set forth below further comments in

support of a finding of utility addressing specific comments set forth in the latest Office Action. Applicants note with appreciation the acknowledgement on p. 3 of the Office Action of three asserted utilities, including screening candidate compounds as inverse agonists, agonists, or partial agonists, and disease/disorder identification and/or selection. The Action at p. 8, lines 1-2, indicates that the asserted utility is credible. Thus, the focus of the rejection is on the specific and substantial portions of the utility requirement.

On page 2, line 21 to page 3, line 1 of the present Action, the rejection states: "The mere identification of the polypeptide as a GPCR is not sufficient to impart any particular utility to the claimed polynucleotide encoding the polypeptide without any information as to the specific properties of the polypeptide." As noted above, the importance of hARE-2 as a GPCR is that GPCRs, such as hARE-2, are known to affect intracellular levels of cAMP or IP₃. The fact that hARE-2 has such an effect is exemplified in the previously submitted Graph 1, thus supporting the utility. Additionally, Applicants disclosure and the knowledge of one of skill in the art, as discussed above, would lead one of skill in the art to the conclusion that hARE-2, by virtue of its effects on intracellular cAMP or Ca²⁺ – which in turn affect neuron viability in the substantia nigra, would be useful in treating disorders such as Parkinson's, or in screening candidate compounds for inverse agonists, agonists, or partial agonists for treating such disorders. Therefore, there is at least one specific, substantial and credible utility.

On page 2, lines 17-18 the action states "there is no well-established utility of the hARE-2 protein since the GPCR family is known for its diversity." As discussed above, Applicants respectfully assert that those of skill in the art would recognize hARE-2 is useful to screen for compounds for promoting the viability of neurons in the substantia nigra and to treat Parkinson's disease. This utility does not rely solely on identification of hARE-2 as a GPCR. Rather, the utility is based on the effect hARE-2 and inverse agonists, agonists and partial agonists thereof have on the level of intracellular cAMP or IP₃ as a GPCR in the substantia nigra. hARE-2's affect on these levels is confirmed by Applicants' previously submitted Graph 1.

In addition to the utility of treating Parkinson's disease, those of skill in the art would also recognize the well-established utility in diagnosing Parkinson's. Those of skill in the art would have known at the time of filing that Parkinson's disease is caused by a loss of neurons in the substantia nigra, as pointed out above. A simple reading of Applicants' disclosure indicates that hARE-2 is selectively expressed in the substantia nigra. Those of skill in the art would have appreciated that a loss of neurons in the substantia nigra – as is found in Parkinson's disease – would be evidenced by a corresponding loss (decrease) of hARE-2 expression in the substantia nigra, for example by using the claimed polynucleotide encoding hARE-2 polypeptide would, therefore, be recognized as useful for identifying loss of neurons in the substantia nigra to diagnose Parkinson's disease. Those of skill in the art at the time of filing would have known how to use the claimed polynucleotide encoding hARE-2 polypeptide to identify the loss of neurons in the substantia nigra. The claimed polynucleotide encoding hARE-2 polypeptide could have been used at the time of filing, for example, as a template for making antisense RNA probes in methods of *in situ* hybridization to detect mRNA encoding hARE-2 polypeptide. See, e.g. Breier (1999) Methods Mol Biol 96:107-117, and references therein. Thus, those of skill in the art would have immediately appreciated that Parkinson's disease is a disorder associated with altered (decreased) levels of the claimed polynucleotide encoding hARE-2 polypeptide and thus would have recognized a specific and substantial utility. The examiner has already acknowledged that such a use would meet the threshold of utility (see p. 5, lines 1-2 March 21, 2003 Office Action, **"A protein of unknown function would have utility if it can be employed as an indicator of a diseased state or of the presence of a disorder."**).

Applicants respectfully assert that *either* of the two foregoing well-established utilities, namely the usefulness of hARE-2 in screening candidate compounds for inverse agonists, agonists, or partial agonists for treating disorders such as Parkinson's disease and the usefulness of hARE-2 in diagnosing Parkinson's disease *in and of itself* is sufficient to meet the threshold of patentable utility.

On page 5, lines 20-21 the Action indicates "Graph 1 (9/19/03) has been provided to establish a specific and substantial utility for hARE-2." (Emphasis added.) Applicants

respectfully disagree with this characterization. Applicants have always maintained, and the specification states that hARE-2 is a GPCR expressed in the substantia nigra and consequently affects the intracellular levels of cAMP or IP₃. Graph 1 merely confirms these assertions. Applicants' September 19, 2003 response forwarding Graph 1 makes this point in stating "While not required to establish utility for hARE-2 GPCR, but rather to indicate the validity of the asserted and well-established utilities for hARE-2 GPCR . . . " (Emphasis added.) MPEP § 2107.02 VI clearly indicates that Applicants may provide new evidence "in support of" utility. Applicants respectfully submit that Graph 1 is such supporting evidence. As such, Graph 1 makes up part of the totality of the record, and must be considered by the Office when evaluating utility. As noted above, prior submission of Graph 1 was sufficient to remove the original utility rejection. Applicants respectfully submit that the asserted and well-established utilities discussed previously and herein satisfy the utility requirement of 35 U.S.C. § 101.

Although the Action and prior actions admit hARE-2 is a GPCR in several locations, the current Action, at page 5, lines 6-7 indicates "[hARE-2] is probably a GPCR but it is unclear from the instant specification whether the hARE-2 protein functions as a GPCR." Applicants respectfully reassert the comments from page 5 lines 5-6 and lines 13-15 of our September 19, 2005 response:

Those of skill in the art at the time of filing would not have had reason to question Applicant's characterization of hARE-2 as a GPCR. . . . The Action simply does not, and cannot, provide evidence that suggests that it is more likely than not that the statement of the Applicant is false. Accordingly, Applicant's assertion that hARE-2 is a GPCR must be accepted by the Office.

To date, there remains no evidence in the record that would lead one of skill in the art to question whether hARE-2 is a GPCR or whether it functions like a GPCR. On the contrary, the record contains arguments and evidence provided by Applicants that hARE-2 would have been believed to be a GPCR at the time of filing. Specifically, Applicants direct the examiner's attention to pages 9-11 (including Annexes 1 and 2) of the September 19, 2005 response. Applicants respectfully assert that although GPCRs are divergent in amino acid sequence as mentioned in the Action, they share common messenger signaling mechanisms, which,

depending on expression location and other factors, result in divergent effects. These common message signaling mechanisms help define GPCRs. Thus, once one of skill in the art concludes hARE-2 is a GPCR, which the Office has not opposed, they would also conclude that hARE-2 would share a common messenger signaling mechanism, i.e. affecting cAMP or IP₃ levels. Thus, hARE-2 would be recognized by those of skill in the art, given Applicants' teachings, as a GPCR that functions as a GPCR. The data presented in Graph 1, further supports the conclusion that hARE-2 acts as a GPCR. Absent any evidence to the contrary, Applicants' assertion that hARE-2 is a GPCR and the logical conclusion that it functions as a GPCR cannot be ignored.

The Action cites Murdoch et al (2000, Blood 95:3032-3042) as reviewing "chemokine receptors, which are structurally similar yet functionally diverse" as standing for the proposition that even if hARE-2 is a GPCR it need not function as one. As discussed above, however, the diversity of these groups as discussed in Murdoch et al. does not refer to signaling. The report in Murdoch et al. that chemokine receptors affect the level of cAMP or IP₃ in a cell is consistent with Applicants' disclosure that hARE-2 is a GPCR that affects the level of cAMP or IP₃ in a cell. Furthermore, although the cellular responses to modulation of GPCRs generally may be diverse, Murdoch et al. indicate that the cellular response to modulation of a particular GPCR can be predictable. Thus, modulators of hARE-2 affecting cAMP or IP₃ in a neuronal cell of the substantia nigra can be predicted to modulate the viability of the cell in view of Hulley et al (1995) European Journal of Neuroscience 7:2431-2440 and Hirsch et al. (1997) J. Neural Transm. Suppl. 50:79-88.

The Action, continues to indicate functional diversity as a reason for lack of utility in stating "Ji et al (1998, Journal of Biological chemistry 273:17299-17302) review the functional diversity among the structurally related G protein-coupled receptors." However, the functional diversity discussed in Ji et al. is in reference to secondary messengers *additional* to the common cAMP and IP₃ messenger mechanisms. The additional messengers are not inconsistent with Applicants' disclosure that the GPCR, hARE-2, affects the level of cAMP or IP₃ in a cell.

The Action notes at page 6, lines 11-14:

It would have taken significant research to determine the role of hARE-2 in substantia nigra and the role of hARE-2 in a disease such as Parkinson's disease and only once these roles were determined, then hARE-2 could be used to screen for compounds to treat the disease.

Applicants respectfully assert that the present application does disclose the role of hARE-2 in the substantia nigra and that those of skill in the art at the time of filing, in view of Hulley et al (1995) European Journal of Neuroscience 7:2431-2440 and Hirsch et al. (1997) J Neural Transm Suppl 50:79-88, would have immediately appreciated the role of hARE-2 in Parkinson's disease. The present application discloses hARE-2 affects the level of cAMP or IP₃ in substantia nigra. Those of skill in the art would have immediately appreciated that a modulator of hARE-2 is useful to treat Parkinson's disease. Those of skill in the art, at the time of filing, would further have immediately appreciated that the claimed polynucleotide encoding hARE-2 polypeptide is useful in identifying a loss (decrease) of neuronal cells in the substantia nigra in methods of diagnosing Parkinson's disease.

Additionally, Applicants respectfully assert that any experimentation required would not be significant as suggested by the Action, and certainly is not undue. Applicants respectfully submit that determining the role of hARE-2 in Parkinson's disease is the biological equivalent of finding and using a light switch. Once you have found the light switch in the dark, it is a routine exercise to determine whether you need to flip the switch up or down to turn the light on or off. Applicants respectfully submit that in associating hARE-2 with the substantia nigra, and consequently Parkinson's disease provides the location of the biological light switch; once found, those of skill in the art will readily be able to assess whether to flip the switch up or down without undue or significant experimentation.

As indicated above, a rejection based on lack of utility cannot be maintained if the invention has a well-established utility. Here, the application discloses hARE-2 affects the level of cAMP or IP₃ as a GPCR in the substantia nigra. Hully et al. and Hirsch et al. clearly indicate that those of skill in the art knew, at the time of filing, that receptor that affects the level of

cAMP or IP₃ in cells in the substantia nigra was useful for screening compounds for promoting viability of neurons of the substantia nigra and accordingly to treat Parkinson's disease.

On page 8, lines 1-2 of the Action, the Examiner acknowledges this utility is credible. Applicants respectfully assert that the utility is specific to hARE-2, the substantia nigra, and the treatment of Parkinson's disease. The utility is substantial because it relates to the very real world problem of treating Parkinson's disease. Applicants respectfully assert that the reasoning presented herein and in prior responses clearly establishes a well-known utility for the claimed polynucleotide encoding hARE-2.

Finally, page 9, lines 11-13 of the Action state:

the skilled artisan would not know if it was desirable to identify drugs that agonize or antagonize hARE-2 as treatment for disorders of the substantia nigra.

The specification teaches the claimed polynucleotide encoding hARE-2, which is a GPCR selectively expressed in the substantia nigra affecting the level of cAMP or IP₃ in a cell, is useful for screening candidate compounds as agonists, partial agonists and inverse agonists of hARE-2. In view of the teachings of Hulley et al. and Hirsch et al. those of skill in the art, at the time of filing, would have immediately appreciated that the group of agonists, partial agonists and inverse agonists of hARE-2 encompasses compounds useful for the treatment of Parkinson's disease.

Claims 77-101 also stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement on the basis that the claims allegedly lack utility. In light of the argument above, Applicants respectfully assert that those skilled in the art would recognize both the utility of the invention and how to use it. Moreover, methods for screening for modulators of GPCRs were well known in the art at the priority filing date of the present application. Some such methods were described in the priority applications. See, for example, Sections D.1. and D.2. on pages 15-17 of Provisional Application no 60/136,436 filed May 28, 1999. See also, for example, Lazareno (1999) *Methods Mol Bio* 106:231-245 and Smith et al. (1993) *Appl Biochem Biotechnol* 41:189-218 (e.g. pp.191-192) and Zhang (1998) *Methods Mol Bio* 105:77-87 (e.g.

Section 1.1 on pages 77-78), and references therein. Applicants therefore respectfully request withdrawal of the rejection based on 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101 and § 112, first paragraph. Further, Applicants assert that the claims are in condition for allowance, and respectfully request notification to that effect.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,
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